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**Implication of depleted uranium in human carcinogenesis with a glance to implementation of novel and reliable experimental models**

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**Abstract**

The recent acknowledgement of Depleted Uranium (DU) munitions utilization in the Ukrainian conflict has sparked renewed apprehensions regarding the safety of DU, its toxicological profile, and the health ramifications of exposure. Historical data from conflicts like the Gulf War, Bosnia, and Kosovo have recorded an upsurge in neoplastic ailments among soldiers in close proximity to DU deployment.

Nevertheless, establishing a direct causal connection between DU exposure and the development of neoplastic diseases remains elusive, as indicated by meta-analyses and studies on animal models. We posit that the absence of a conclusive causal correlation between DU exposure and neoplastic diseases may be ascribed to the constraints of current study models, which fail to encapsulate the intricate interactions between DU and the human immune system, pathophysiology, particularly in the context of chronic, low-level exposure. Nowadays, evidence suggests that DU exposure contributes to a cumulative immunotoxic effect, culminating in a compromised immune surveillance system and an escalated risk of neoplastic diseases over time. To investigate this hypothesis, we advocate for the advancement of pioneering research models, such as human *ex-vivo* body-on-a-chip systems, which can more accurately replicate the human physiological response to DU exposure and cancer pathophysiology. These models should encompass the examination of immune system modifications along with the potential for DU to interact with diverse organs and tissues, thereby furnishing a more comprehensive understanding of the enduring health impacts of DU.

**Depleted uranium and its use for civil and military purposes**

Depleted Uranium (DU) is a chemical compound of significant interest in the scientific realm, characterized by unique chemical and physical properties. This compound has garnered considerable attention due to its versatile applications in both civilian and military domains. The present exposition aims to examine the distinctive attributes of DU and explore its multifaceted applications, with a particular focus on its role within the medical context. DU is derived through an enrichment process, during which the concentration of the fissile isotope uranium-235 (U-235) is intentionally reduced compared to natural uranium. The latter typically contains around 0.7% U-235. Sophisticated techniques such as gaseous diffusion or centrifugation are employed to separate U-235 from the more abundant uranium-238.[1] From a physical perspective, depleted uranium is a heavy metal exhibiting a gray-silver coloration. Its high density and intrinsic radioactivity render it a unique material.[2] In the realm of medicine, DU assumes a fundamental role. Its radiation-absorbing capacity makes it ideal to produce radiographic and radiopaque screens, employed to safeguard medical personnel and patients during radiological imaging procedures, including X-rays and Computed Tomography (CT) scans.[2] Additionally, DU finds utility in brachytherapy, a cancer treatment technique wherein radioactive sources containing this material are placed inside the patient's body to directly irradiate cancer cells.[3]
Within the military sector, DU is utilized as a penetrator core in armor-piercing munitions. Its high

density and hardness render it extraordinarily effective in perforating armored vehicles and fortified structures. When a projectile with a depleted uranium core strikes a target, its significant velocity and kinetic energy enable it to penetrate the material, leading to explosions or fires within the vehicle or structure.[3] It is essential to underscore that the military use of depleted uranium has increasingly drawn attention and debate due to concerns regarding its potential[4] impact on human health and the environment stemming from the inhalation of airborne particles containing depleted uranium, encompassing issues ranging from radioactive contamination to a potential elevation in the risk of cancer.[3] The utilization of DU-based weaponry immediately sparked significant interest and public debate, particularly following their initial deployment during the first Gulf War in 1990-1991. This interest has been magnified by the increasing reports of negative health effects on military personnel, known as the so-called 'Gulf War Syndrome'.[3] The symptomatology associated with Gulf War Syndrome has been characterized by a wide range of disorders, including chronic fatigue, gastrointestinal disturbances, cognitive impairments, arthritis-like symptoms, and neurological disorders.[3] Epidemiological studies conducted on Gulf War veterans have identified a significant increase in neurodegenerative diseases, autoimmune disorders and cancer rates among those potentially exposed to depleted uranium.[5] This will be further discussed in one of the next paragraphs.

Microscopic particles of DU released during the use of DU-containing munitions can be inhaled or ingested. While DU emits alpha and beta radiation with lower penetration power compared to natural uranium, the key concern lies in its cytochemical toxicity and, in particular, its ability to interfere with calcium metabolism and generate highly reactive free radicals within the human body. These processes can contribute to cellular damage and systemic inflammation, creating an environment conducive to the development of both acute and chronic diseases.[6] Furthermore, it should be emphasized that DU has also been associated with environmental concerns, with potential long-term impacts on ecosystems and water resource contamination.[7] Scientific interest and public attention regarding DU remain high, as the long-term effects on both the environment and human health continue to be subjects of research and discussion in various international contexts.

**Pathways of depleted uranium entrance and accumulation in human body**

DU presents various pathways through which it can expose individuals, each with distinct health impacts. To fully comprehend the risks, it is essential to examine these modes of exposure.

External exposure to DU is primarily due to the alpha and beta radiation emitted by its decay products. However, such exposures are generally limited, with the tegumentary system, e.g. the skin, being the primary target,[1] a scenario notably emphasized in military contexts, where the extensive use of DU

munitions can generate particulate dust and fragments that can lead to widespread distribution of the contaminant in the surrounding environment. Internal exposure to DU plays a crucial role and is possible through three main pathways. The first pathway involves the gastrointestinal system by the ingestion of water and food contaminated with DU. Such ingestion can occur through manual soil contamination or the consumption of animal products from areas where animals have grazed on contaminated land.[8] Drinking water constitutes one of the primary natural exposure route to DU.[9] Contamination of drinking water can result from various sources, including the dispersion of DU into the soil, as previously mentioned.[10] However, it should be noted that another important exposure route to DU is through the respiratory system, by the inhalation of DU-containing particles, a significant phenomenon in both conflict situations and other circumstances. This form of exposure to DU aerosols can originate from two main sources: the natural presence of DU in the environment and the use of munitions containing DU. When DU munitions strike a target, they produce dust particles of varying sizes.[11] This type of contamination can have significant environmental implications, given the extended half-life of DU nanoparticles.[12]

After the inhalation of such particles, they can quickly access the bloodstream, spreading throughout the body and accumulating in various organs and tissues. It is important to note that DU has a pulmonary half-life of approximately 4 years, which may contribute to the onset of both local and systemic inflammatory processes.[3,13] A relevant aspect is the retention of DU in tissues and organs, particularly in bones and bone marrow, even after the cessation of direct exposure.[14,15] This characteristic necessitates constant attention to the management of DU-related risks and the protection of public health. The pathways through which DU exerts its toxicity *in vivo* can be manifold, related to both its (though weak) radioactive activity and its intrinsic chemical properties.[3]

**The “Gulf War Illness”, a novel nosographic entity**

It is widely acknowledged that the effects of Gulf War Illness (GWI, also called “Gulf War Syndrome”) are prevalent among veterans who participated in military operations between 1990 and 1991, involving a significant percentage of them.[16] Recent researches have continued to strengthen the correlation between exposure to various environmental contaminants, including DU, and the onset of symptoms associated with GWI.[16,17] These studies have highlighted how the accumulation of such contaminants can trigger systemic inflammatory reactions, characterized by the abundant release of inflammatory cytokines such as IL-1β, INF-γ, and IL-6.[18-20] These inflammatory reactions can turn into a chronic inflammatory state, particularly in the Central Nervous System (CNS), and mostly contribute to dysfunctions of veterans'

innate immune system.[21]

As mentioned earlier, veterans deployed in conflict zones appear to be more susceptible to developing chronic multi-symptom illness compared to those not deployed.[22] This trend is supported by experimental evidence, both *in vivo* and *in vitro*, demonstrating how activated pro-inflammatory mechanisms can explain the wide range of symptoms associated with GWI.[16] Furthermore, it should be emphasized that the accumulation of environmental toxins in tissues could contribute to chronic inflammatory processes. For example, DU can accumulate in tissues following repeated exposures at low levels, both through inhalation and the ingestion of contaminated water or food.[3,23,24]

**Depleted uranium and cancer**

While the aforementioned information seems to confirm a role for DU in the onset of a wide spectrum of symptoms in Gulf War veterans, in other theaters of war where DU-containing munitions have been used, data obtained from retrospective meta-analyses may appear contradictory or, in any case, insufficient to assert an unequivocal direct causal link between DU exposure and the emergence of malignant neoplasms. Recent meta-analyses conducted on military personnel and the civilian population in Bosnia and Kosovo during the period from 1995 to 2015 have shown a concerning trend of increased incidence of neoplasms precisely during the time and in the locations where the aforementioned conflicts occurred.[25,26] However, several independent studies have sought to delve into the correlation between DU exposure and the onset of neoplasms.[26-28] Nonetheless, they all agree that establishing an unequivocal causal link is challenging, despite the clear absolute increases in the incidence of pathologies observed in the analyzed patient cohort, based on the currently available data.[26-28]

A thorough review of data from the Bosnia and Kosovo conflicts reveals the frequently conflicting nature of the evidence.[25] It is emphasized, in fact, that the military deployed during the aforementioned wartime operations were exposed to radiation doses well below the minimum alert thresholds, with an estimated overall average value of about 0.15 mSv, which is 15% of the effective dose limit for the general population in one year, and with an overall percentage below 10% of the dose absorbed by an individual during diagnostic procedures such as CT scans.[4,25,29] This effectively rules out a direct causality between the malignancies observed in an increasing trend and the direct action of ionizing radiation, a fact also supported by sample analyses conducted on 11 Bosnian sites (though limited by the presence of

unexploded ordnance and mines in much of the territory) seven years after the end of the conflicts, which did not show significant variations between the isotopes 235U, 236U, and 238U and natural uranium.[25,30] Therefore, the causality link was sought in the exposure to nanoparticles and heavy metals.[25] Evaluating the preferential contact and deposition districts with the particles in question, such as airways, bones, and kidneys, it was not possible, based on the available metadata analysis, to confirm a direct causality between the contact or accumulation site and the onset of neoplasms *in situ* (Table 1).[25]

Although the opinion of the consulted scientific commissions effectively indicated the risk level of DU ammunition as negligible, the NATO Command of Military Medicine Services (COMEDS) and the Italian Ministry of Defense Commission both stated that it was necessary to conduct further epidemiological investigations on the affected sites and personnel involved and that a possible link with the onset of hematologic neoplasms such as Hodgkin's lymphoma could not be excluded.[25,36,37]

In addition to the data cited above and the meta-analyses carried out, an interesting study is added which reports the preliminary results of an analysis conducted on the incidence of malignant tumors in young Italian soldiers sent on missions abroad in the period 1996-2012.[38] The analysis was conducted by the Parliamentary Commission of Inquiry into Depleted Uranium and Vaccines (CUC) and involved 3,663 cases of malignant tumors among male servicemen aged between 20 and 59. The soldiers were divided into two groups: missionaries (874 cases) and non-missionaries (2,789 cases).[38]

Preliminary results have highlighted significant excess risks in missionaries for specific neoplasms, such as blood and lymphatic system and Hodgkin's lymphoma (Table 2).[38]

However, the analysis also highlighted, consistently with what has been reported by other independent studies, the need for further in-depth investigations to fully understand the impact on the health of Italian and foreign soldiers on missions abroad from 1973 to 2017 and to adopt adequate preventive measures.[38]

Nevertheless, all retrospective involved studies agree that several gaps and inconsistencies in data collection do not allow for the establishment of the direct causality mentioned above,[25-28] although they do highlight an increasing trend for some tumor pathologies.[25] Among the main limitations identified in various studies and reports are the small sizes of some cohorts, the incomplete recovery of incidental cases in the extended follow-up of the Italian cohort, and the short follow-up period in some studies.[25,39]

**Carcinogenesis: a multi-step process**

Considering the foregoing, it becomes essential to consider carcinogenesis in its utmost complexity. The structural hierarchy of the human body reveals an intricate order, where organs arise from the complex organization of tissues. These tissues, in turn, emerge from the combination of cells. Although tissues are categorized into four main types (epithelial, connective, muscular, and nervous), they share and differentiate due to the process of differentiation of undifferentiated cells (often erroneously referred to as 'stem cells'). In general, all tissues harbor undifferentiated cells in varying quantities, depending on the anatomical context and other biological variables, and the specific tissue function.[40]

Alterations affecting the complex system that regulates cell divisions and cell precursor specialization, following multifactorial phenomena, can lead to dysplastic and neoplastic phenomena within the tissue.[40] This process unfolds through three fundamental stages: in the initial phase, primary genetic alterations in DNA occur, triggering cell transformation; subsequently, in a stage referred to as promotion, the accumulation of additional genetic and epigenetic mutations becomes evident, allowing potentially tumorous cells to multiply uncontrollably.[40] Finally, in the advancement phase, cells acquire the ability to escape the immune system to avoid its components, especially those of the innate immune system, and to undergo metastatic infiltration into surrounding tissues.[40]

Carcinogenesis is significantly impacted by the immune system, particularly Natural Killer (NK) lymphocytes, which are crucial for detecting and destroying emerging tumor cells before they can proliferate invasively.[41] However, deficiencies in immune cells, whether quantitative or qualitative, may impede this intricate process, offering a window for tumor progression. This discourse delves into the potential contribution of DU exposure to carcinogenesis, particularly in its promotional and progressive phases, entailing epigenetic modifications and the immune system compromise.

A nuanced exploration of DU exposure necessitates an examination of contamination in war theaters and adjacent regions, along with the intricate pathways through which DU infiltrates and deposits within the human body. DU, originating from weapon detonations in war zones, engenders nanoparticles capable of traversing considerable distances, settling in soil, and permeating groundwater, thus perpetuating contamination due to the enduring half-life of DU nanoparticles.[42] Studies indicate that even brief exposure to DU heightens the risk of cancer through epigenetic alterations, impacting vital organs such as the kidneys and bones.[40] Scientific consensus recognizes the occurrence of diverse neoplasms throughout human life, mitigated by immune surveillance mechanisms before clinical manifestations.[40]

Debate over the causes of cancer ranges from attributing it to random genetic mutations to considering the

influence of environmental and lifestyle factors.[40] DNA mutations, arising from random genetic errors during cell replication, are deemed inevitable irrespective of healthy habits or environments.[43] The chaperoning system, essential for maintaining protein balance and crucial cellular functions, includes molecular chaperones, co-chaperones, chaperone co-factors, and their interactors/receptors.[40] While pivotal for health, aberrant chaperones or their involvement in pathogenic pathways, such as carcinogenesis, can prove detrimental to physiological processes.[40]

Research has underscored the potential for depleted uranium to contaminate the organs and tissues of individuals, including military personnel in war zones, through various exposure pathways.[1,44] Among the preferential sites for the deposition and accumulation of DU nanoparticles, in addition to primarily exposed organs such as the upper airway organs and lungs, it is essential to consider kidneys, bones and bone marrow.[40] The biodistribution of DU nanoparticles is quite ubiquitous, as they can easily reach the bloodstream from the lungs and, once they reach the aforementioned organs, they can settle there for years or putatively decades.[40] Even the liver, the reproductive system, and sensory organs such as the eyes are not exempt from accumulating of DU particles.[40] Of relevance for our discussion is undoubtedly the bone marrow.

**Depleted uranium induces bone marrow damages**

Bone marrow, one of the main actors on the stage of our body, is the vital factory for blood cells. Unlike well-confined organs, the marrow is not designated to a single location but hides in various recesses of our skeleton. It is divided into three structurally and functionally different forms: red, yellow, and gelatinous (the latter is only found in older individuals).[45] Red bone marrow assumes the role of the epicenter of hematopoiesis. It mainly resides in the central parts of our body, between the trunk bones and the major limb bones in adults. In contrast, yellow marrow appears in mature adults, gradually replacing red marrow due to the accumulation of adiposity, especially in the bones of the limbs.[45,46]

Red bone marrow, with its dense network of blood vessels, performs hematopoietic function generating all the cellular components of blood tissue. This process starts with an undifferentiated mother cell called hematopoietic stem cell. Among white blood cells, we find granulocytes and agranulocytes, along with lymphocytes divided into B cells, T cells, and NK cells. To ensure stemness potential, as in all other body districts, the progenitor stem cell undergoes a division process aimed at preserving stem potential, and

then one of the two daughter cells undergoes a differentiation process.[45,46]

Recent studies conducted both *in vivo* and *in vitro* have confirmed that DU indeed has a significant impact on the cells of the immune system, exerting its toxic potential through multiple pathways, including DNA damage, apoptotic induction, altered gene expression, and disruption of cellular metabolic activities.[47] Therefore, experimental evidence gathered demonstrates that there could indeed be a significant impairment of the immune response, especially regarding the role of the innate immune response, in which NK cells play a key role.[23,48]

Considering the aforementioned, it is plausible to consider that the toxicological damage exerted by DU primarily occurs in the initial and promotional stages. Over the years, these studies, recently summarized by an all-encompassing review work, have confirmed that damage to the immune system can be concrete and have significant implications for the health of exposed individuals.[40,44,47] Research conducted by various independent groups confirms that DU exposure can indeed negatively influence the human immune system.[47] However, DU immunotoxicity is a complex phenomenon that requires careful evaluation. Cellular studies indicate that DU can affect immune cells at non-cytotoxic levels, altering gene expression and signaling mechanisms.[47] This would be consistent with a potential lowering of the immune defenses of the exposed individual, unable to promptly counter the onset of dysplastic and neoplastic processes in the early stages of these pathologies. Studies on animal models suggest DU accumulation in immune tissues and changes in immune cell function. However, it is challenging to directly extrapolate results from animals to humans.[47] Evidence in human cells and epidemiological studies suggest that DU can influence cytokines, DNA damage, and cell counts, but further research is needed to fully understand the effects of human DU exposure, especially considering co-exposure to other toxic metals.[47,49]

**Bone marrow damage and lowering of immune defenses: possible hypothesis**

The dissemination of DU within the organism occurs extensively, with a pronounced propensity to accumulate in highly vascularized compartments. The bone marrow, therefore, emerges as a particularly vulnerable district to prolong DU accumulation. Epigenetic alterations arising in precursor cells of the immune system can, over time, lead not only to the formation of cancerous cells on-site but also to a functional weakening of the immune system. The latter significantly diminishes as it is deprived of a

substantial portion of innate immune cells, including NK cells, crucial for monitoring the organism and promptly intervening in the event of neoplastic pathologies.[40]

In this context, our hypothesis posits that the observed immunosuppression could act as a critical facilitator in the pathogenesis of various neoplasms. Given that a robust immune system is paramount for the identification and eradication of aberrant neoplastic cells, its impairment due to DU accumulation may result in an increased vulnerability to neoplastic transformations. This could manifest as an acceleration in the development of pre-existing neoplastic conditions or, perhaps, a lowering of the threshold at which oncogenic triggers may initiate neoplasia.

In attempting to establish scientific coherence among the increasing tumor types observed in individuals exposed to DU, often not directly correlated to a clear cause (DU exposure – onset of specific tumor types), it is possible to identify the potential weakening of the immune system in exposed individuals, due to the preferential accumulation of DU in the bone marrow, as a plausible cause of neoplastic pathologies. This relationship could explain the onset of such pathologies in anatomical sites and etiopathological contexts not typically closely interconnected.[25,40]

The human body routinely accumulates 'errors' during normal cell turnover. However, when these anomalies lead to the appearance of cells with altered phenotypes, a well-functioning immune system generally recognizes them promptly, subsequently inducing apoptosis. In the wake of DU exposure, this detection and resolution mechanism may be compromised, allowing the nascent neoplastic cells to escape immunosurveillance. This hypothesis can be further supported by the documented presence of hematological tumors, even in children, where the immune system is particularly susceptible to epigenetic alterations and environmental stressors.[40] Furthermore, the possibility that DU could act as a potential trigger for neoplastic diseases should be considered, particularly considering its ability to induce a pro-oncogenic environment through direct genomic instability and indirect immunosuppressive pathways.

**Suitable experimental models**

The extensive body of research on DU underscores the potential risks associated with its use, particularly in military contexts where DU munitions are deployed. Our comprehensive analysis reveals that direct exposure to DU, primarily through nanoparticles resulting from munition detonation, presents a significant concern for human health. The data, derived from a combination of *in vitro* and *in vivo* studies, as well as retrospective analyses of exposed populations, consistently point to the need for a

precautionary approach in managing DU's potential carcinogenic effects.[3]

Despite the compelling evidence, establishing a direct causal link between DU exposure and the onset of neoplastic pathologies remains elusive. The challenges are manifold, including the diversity of reported neoplastic diseases, the limited follow-up of affected individuals, and the incomplete territorial sampling analyses in vast war zones. These factors contribute to an incomplete understanding of DU's long-term effects, necessitating the development of more sophisticated research models.

While indicative of molecular alterations and cellular dysregulation due to DU exposure, current animal studies fall short of providing a comprehensive picture. They lack an integrative approach that can correlate immune system changes with the effects on other organs and tissues. To bridge this gap, we propose the use of human *ex-vivo* body-on-a-chip systems, which promise to offer a more detailed representation of the body's response to DU and serve as a crucial link between traditional culture models and *in vivo* animal systems.[47,50,51] The urgency for certainty in understanding DU's long-term toxicological effects is heightened by its routine use in both civilian and military applications. This necessitates not only the formulation of robust experimental hypotheses but also the implementation of effective strategies to confirm or refute these hypotheses. Our multidisciplinary and cross-sectoral approach, involving collaboration between medical professionals and researchers in biotechnology and bioengineering, is pivotal in achieving a comprehensive understanding of DU's impact on health. This collaborative effort enables a nuanced exploration that transcends disciplinary boundaries, providing valuable insights into the complex interplay between DU exposure and human health.

In the aftermath of our exhaustive examination concerning the cytotoxicity of DU and its ramifications for human well-being, we amalgamate several conjectures that arise from the data. Initially, we postulate that DU exposure contributes to carcinogenesis via epigenetic modifications and compromise of the immune system, particularly impacting the hematopoietic system in both children and adults.[40] Secondly, we posit that the enduring accumulation of DU nanoparticles in the body, notably in highly vascularized tissues such as the bone marrow, kidneys, and bones, could result in a persistent susceptibility to neoplastic ailments, even years after the initial exposure.[3,40] Thirdly, we advocate that the current research paradigms, encompassing *in vitro* and *in vivo* animal studies, are inadequate in elucidating the intricate human physiological response to DU exposure, and we endorse the adoption of advanced human *ex-vivo* body-on-a-chip systems to bridge this disparity.[47,50,51] Fourthly, we contemplate the potential of DU to instigate a persistent inflammatory condition, particularly in the CNS, which might contribute to the extensive array of symptoms linked to GWI and other multi-symptom illnesses in veterans.[15,17,20] Lastly, we acknowledge the necessity for a multidisciplinary and cross-sectoral approach to comprehensively comprehend the impact of DU on health, accentuating the principles of precaution and prevention in light of the prevailing uncertainties regarding DU's carcinogenic potential. These conjectures underscore the exigency for robust experimental hypotheses and strategies to affirm or disprove the potential health

hazards associated with DU exposure, steering future research towards a more holistic and comprehensive grasp of its enduring effects (Figure 1).

## Conclusions

Upon reflection, the body of evidence, though not yet conclusive, raises substantial apprehensions regarding the potential health ramifications of DU exposure. The amassed data implies a plausible association between DU and the occurrence of neoplastic diseases, conceivably influenced by the immunosuppressive effects of DU accumulation in the bone marrow. This postulated mechanism, wherein DU may expedite or even initiate the development of neoplasms, warrants thorough scientific scrutiny.

It is imperative, therefore, that forthcoming research on DU exposure and its health outcomes is executed with unwavering scientific integrity and a distinct demarcation from any conflicts of interest. This necessitates methodologically robust studies that are not only scientifically sound but also ethically responsible. Our article has endeavored to expound upon the current comprehension and to underscore the urgent necessity for further exploration in this domain. The potential implications of our formulated hypothesis that DU exposure could contribute to an increased incidence of neoplastic diseases through immune system compromise must be meticulously examined.

As we advocate for sustained scientific research, we underscore the utmost importance of upholding scientific competence and courage, particularly when navigating the intricate and frequently contentious field of DU-related research. The intricate web of interests that characterizes this domain must not be allowed to entangle the pursuit of knowledge or impede the progress of independent scientific discovery.

In championing scientific rigor, it is imperative that future endeavors in DU research not only adhere to the highest standards of methodological quality but also embody ethical principles and remain impervious to undue external influences. The stakes are high: only through such a commitment can we truly assess the risks of DU and protect the health and well-being of individuals and communities worldwide.

Ensuring that the scientific narrative remains pure and unadulterated by vested interests is not just a matter of academic integrity, but it is a moral imperative with real-world consequences.

Our call to action is clear: we must foster an environment where scientific inquiry into DU and its potential link to neoplastic diseases is not only possible but thrives, free from the constraints of bias and motivated by the sole purpose of uncovering the truth. Only through such concerted and principled efforts we can hope to elucidate the full impact of DU exposure and safeguard future generations from its possible hazards.

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| **Cancer site** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **SIR *** | **CI (95%)** | **SIR** | **CI 95%** | **SIR** | **CI 95%** | **SIR** | **CI 95%** | **SIR** | **CI 95%** |
| All cancers | 0.48 | 27.79 – 51.35 | 0.85 | 0.73 - 0.99 | **1.19** | 0.80 – 1.80 | 0.90 | 0.70 – 1.10 | **1.11** | 0.93 – 1.31 |
| Colorectal cancer | - | - | - | - | **2.00** | 0.51 – 7.78 | **2.25** | 1.19 – 4.25 | 0.52 | 0.24 – 1.15 |
| Lung cancer | - | - | 0.48 | 0.23 - 0.89 | **1.25** | 0.18 – 7.08 | 0.40 | 0.10 – 1.52 | 0.87 | 0.28 – 2.04 |
| Melanoma | **-** | - | - | - | 0.90 | 0.10 – 3.30 | 0.70 | 0.20 – 1.70 | **1.36** | 0.78 – 2.22 |
| Bone cancer | - | - | - | - | - | | **6.0** | 1.60 – 15.3 | - | - |
| Thyroid cancer | - | - | - | - | - | | **1.10** | 0.19 – 5.89 | **1.60** | 0.43 – 4.09 |
| Bladder cancer | - | - | - | - | **2.90** | 0.40 – 11.0 | **2.20** | 0.90 – 4.50 | **1.98** | 0.85 – 2.90 |
| Kidney cancer | - | - | - | - | - | | **1.10** | 0.10 – 4.10 | 0.57 | 0.12 – 1.66 |
| Testicular cancer | - | - | - | - | **1.90** | 0.80 – 3.70 | **1.20** | 0.80 – 1.80 | **1.02** | 0.66 – 1.50 |
| Brain cancer | - | - | - | - | **1.20** | 0.20 – 3.40 | **1.20** | 0-50 – 2.20 | 0.73 | 0.32 – 1.44 |
| Haemolymphatic cancer | - | - | 0.95 | 0.63-1.28 | **1.40** | 0.50 – 3.30 | **1.08** | 0.61 – 1.90 | **1.16** | 0.66 – 1.77 |
| Hodgkin's lymphoma | **2.36** | 5.39 – 18.23 | - | - | **1.90** | 0.20 – 6.70 | **1.00** | 0.20 – 2.90 | - | - |
| Non- Hodgkin's lymphoma | 0.94 | 3.0 – 13.71 | - | - | 0.83 | 0.11 – 6.14 | 0.80 | 0.20 – 2.30 | - | - |
| Leukemia | **1.78** | 0.21 – 6.28 | 0.63 | 0.20-1.46 | **4.0** | 1.28 – 14.3 | **1.40** | 0.40 – 3.50 | **1.25** | 0.54 – 2.46 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Liver | - | - | - | - | - | - | **1.08** | 0.0 – 9.8 | 0.00 | 0.00 - 3.67 |
| Liver (not primary) | | | | | | | **3.3** | 0.1 – 18.6 | - | - |
| Salivary glands | | | | | | | **3.6** | 0.1 - 19.9 | - | - |
| | **(31)** | | **(32)** | | **(33)** | | **(34)** | | **(35)** | |
| | **References** | | | | | | | | | |

**Table 1.** Standardized Incidence Ratio (SIR), a metric that compares the observed number of cases in a specific group to the expected number of cases based on a standard population, adjusting for age differences to ensure accurate comparison, that in this table describe pathologies on different cohorts of patients who in the period 1999 to 2016 were employed as armed forces in the war scenarios (NATO peacekeeping forces in Bosnia and Kosovo from 1996 to 2016 and military forces deployed to the Balkan region from 1993 to 2001). CI = confidence interval. The table reports the results deriving from studies on the incidence of tumors of the Balkans.

| | **Cancer site** | **SIRm**(×100)** | **CI 90%** |
|---|---|---|---|
| Aeronautics | Melanoma | - | - |
| | Kidney cancer | - | - |
| | Testicular cancer | - | - |
| | Colorectal cancer | 230.6 | 62.9 – 596.0 |
| | Bladder cancer | 244.9 | 137.4 – 405.4 |
| | Stomach cancer | - | - |
| | Leukemia | - | - |
| | Hodgkin Lymphoma | 187.7 | 88.1 – 352.5 |
| | Non-Hodgkin Lymphoma | - | - |
| | Thyroid cancer | 154.4 | 90.9 – 235.1 |
| | All Cancers | **126.7** | **107.9 – 147.9** |
| | | | |

| | | | |
|---|---|---|---|
| Carabinieri | Melanoma | 199.4 | 115.0 – 323.0 |
| | Kidney cancer | - | - |
| | Testicular cancer | 266.3 | 176.5 – 387.0 |
| | Colorectal cancer | 330.6 | 112.9 – 756.4 |
| | Bladder cancer | - | - |
| | Stomach cancer | - | - |
| | Leukemia | - | - |
| | Hodgkin Lymphoma | 187.3 | 87.9 – 351.8 |
| | Non-Hodgkin Lymphoma | 238.1 | 81.3 – 544.9 |
| | Thyroid cancer | 377.0 | 283.5 – 492.4 |
| | All Cancers | **152.8** | **134.0 – 173.7** |
| Navy | Melanoma | - | - |
| | Kidney cancer | 1187.3 | 644.2 – 2014 |
| | Testicular cancer | - | - |
| | Colorectal cancer | - | - |
| | Bladder cancer | - | - |
| | Stomach cancer | - | - |
| | Leukemia | - | - |
| | Hodgkin Lymphoma | - | - |
| | Non-Hodgkin Lymphoma | - | - |
| | Thyroid cancer | - | - |
| | All Cancers | **61.1** | **51.0 – 72.6** |
| Army | Melanoma | 153.5 | 112.9 – 204.4 |
| | Kidney cancer | - | - |
| | Testicular cancer | - | - |
| | Colorectal cancer | 223.0 | 131.9 – 354.6 |
| | Bladder cancer | - | - |
| | Stomach cancer | 216.7 | 135.9 – 329.2 |
| | Leukemia | 142.2 | 107.5 – 185.4 |
| | Hodgkin Lymphoma | 104.5 | 82.2 – 132.6 |
| | Non-Hodgkin Lymphoma | - | - |
| | Thyroid cancer | 130.6 | 102.6 – 164.2 |
| | All Cancers | **116.2** | **108.1 – 125.6** |

**Table 2** **SIRm: Standardized incidence rate (×100), missionaries vs. non-missionaries. The table summarizes the main tumor sites highlighted by the study, the data are grouped based on the armed corps they belong to, underlining a lack of homogeneity between the various groups analyzed.[38]

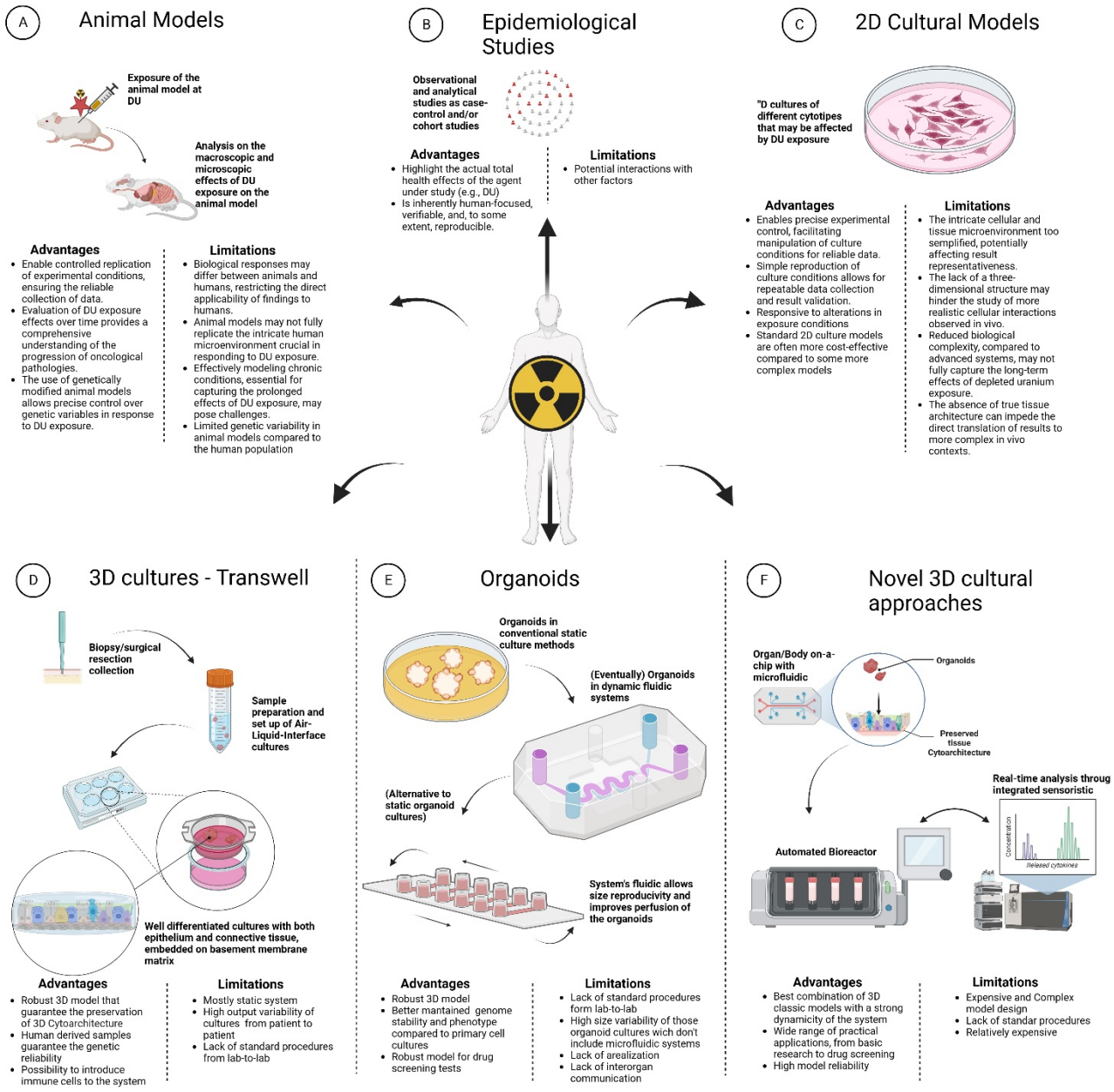


**Figure 1.** Comparative analysis of *in vitro*, *in vivo*, and *ex vivo* methodologies for assessing the potential causal relationship between Depleted Uranium (DU) exposure and the onset of neoplastic pathologies. Given the impracticability of human studies, the research focuses on retrospective analyses and follow-ups of military personnel deployed in theaters of conflict involving the deployment of DU munitions.

Each methodology listed above present pro and cons, suggesting that an integrative approach might be the optimal solution in order to overpass the intrinsic limitations that studies that involves the long term effects of DU carries on. Created with BioRender.com